Stimulants and Tic Disorders

From Dogma to Data

IT IS A simple question. Do psychostimulants worsen tic disorders? In the 1970s and early 1980s, the answer was unequivocally yes. The presence of a tic disorder in a patient, or even a history of tics in a close family member, became a contraindication to prescribing methylphenidate hydrochloride.[1] However, the answer has not remained simple. In this issue of the ARCHIVES, Gadow et al[2] present their longitudinal follow-up of 29 children with attention-deficit/hyperactivity disorder (ADHD) and chronic multiple tic disorder (mostly Tourette syndrome) who were treated for 2 years with methylphenidate. They pose a public health question: "to address the issue of potential tic exacerbation from the standpoint of group data (ie, is treatment ill-advised in this clinic population?), and not to verify possible tic exacerbations in individual children." They conclude that treatment with methylphenidate does not result in long-term exacerbations of motor or vocal tics in prepubertal children, at least when their tics are mildly to moderately severe. This is an important, carefully designed study, which, in conjunction with the complementary reports on this topic in the past decade,[3-5] could lead to a more sophisticated understanding of the relationship between stimulants and tics.

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Though identified in the 19th century, treating Tourette syndrome attracted little medical or scientific interest until the 1960s. The contrast with Parkinson disease may have resulted in the hypothesis that dopamine antagonists would prove helpful in Tourette syndrome. Gratifyingly, the hypothesis was confirmed. Neuroleptic drugs remain the mainstays of treatment for severe tic disorders.[6]

As awareness of tic disorders increased, a worrisome coincidence was noted. Occasionally, stimulant treatment for hyperactivity was followed by motor and vocal tics that endured even when the stimulant was discontinued.[7-9] The parallel with tardive dyskinesia and the elucidation of stimulant sensitization further increased concern. Sensitization is produced by subchronic administration of stimulants, resulting in exaggerated responses to even smaller than usual doses. Perhaps some children who had developed tic disorders might have been spared if they had not been exposed to a psychostimulant.[1]

Opposing the apparently overwhelming logic of this position were a few clinicians who reported that stimulants were well tolerated by many patients with tic disorder.[10,11] However, although these observations were retrospective, 1 such survey was particularly clever. Price et al[12] located 6 pairs of monozygotic twins with Tourette syndrome who were discordant for exposure to stimulants. If stimulants conferred long-term risks to patients with tic disorders, then the treated twins should have had a differential course, with earlier onset, more severe tics, and perhaps more severe residual tic disorders. In fact, the results were almost the opposite. While comparisons could not be validated statistically in such a small sample, there was no clear relationship between the onset of tics and the onset of stimulant treatment. If anything, the treated twins had a tendency toward decreased tic severity in the long-term.

Against this background, Sverd et al[5] began a single-blind comparison of the effects of methylphenidate in children with ADHD and a tic disorder. The publication of their first 4 cases was accompanied by appropriate cautions.[13] It also led my colleague, Josephine Elia, MD, to design a trial that we recently concluded.[3] In the meantime, Gadow et al[4] expanded their sample and used a double-blind design that incorporated multiple observers in the clinic, school, and home. They found robust dose-related improvements in behavior with methylphenidate hydrochloride (at doses of 0.1, 0.3, and 0.5 mg/kg twice daily) together with a "relatively benign," though statistically significant, dose-related increase in motor tic frequency in 1 measure, and no significant worsening in 12 others.

Our data complemented and extended their observations. We included patients with severe Tourette syndrome, and compared placebo with both methylphenidate and dextroamphetamine sulfate with a wide range of doses (eg, 0.4, 0.7, and 1.2 mg/kg twice daily for methylphenidate hydrochloride). At our lowest doses, we also did not detect significant worsening of tic severity for either stimulant, because some children improved and others worsened. However, at higher doses, mean tic severity was significantly increased by 21% (methylphenidate, medium dose) to 25% (dextroamphetamine, high dose). Fortunately, tic exacerbations associated with methylphenidate diminished in most children in time even with continued administration. By contrast, tic severity on dextroamphetamine decreased in the long-term in only 1 child out of 20.[3]

Now Gadow et al[2] provide data that most ratings of tic severity were unchanged after 2 years of methylphenidate treatment, although the 2-minute physician's motor tic count worsened significantly. If these results bring to mind the Heisenberg uncertainty principle, the parallel may be apt. For example, most patients can temporarily suppress their tics with effort, but talking about tics or an awareness of being observed can also worsen tics.[14] Accordingly, quantifying tic disorders remains a daunting challenge.

Patients and their parents have a somewhat easier task. Their questions are: (1) Does methylphenidate improve ADHD symptoms sufficiently to override its effects on tics? (2) Will methylphenidate worsen tics in the long run? The most convincing evidence that the answer to the first question is affirmative in the Gadow study are the low rates of attrition (15%) and of combined pharmacotherapy (only 4 children took anti-tic medications during the follow-up period). These results attest to the overall acceptability of the treatment, the high degree of variability (noise) of tic measurements, and the strength of the therapeutic alliance.

The answer to the second question of long-term effects remains tentative because it is based on so few subjects. However, it is an important negative that stimulant-induced tic sensitization has not been detected in either prospective study.[2,3] Still, stimulants are not tolerated by all tic patients with ADHD. At least 2 of the children in this study discontinued methylphenidate treatment during follow-up, as did one third of our patients, which is consistent with retrospective reports.[10] Thus, physicians will need to learn the limits and risks of stimulants when used in patients at risk of tic disorders, much as we manage the adverse effects of many other useful medications. The admonition to "start low, go slow" applies.[6]

Learning the limits of available medications and exploring future drugs may be facilitated by the recently created Research Units for Pediatric Psychopharmacology. These 7 units funded by the National Institute of Mental Health, Bethesda, Md, are charged with conducting collaborative multisite studies with difficult to recruit samples. Many possible studies are worth considering. In the case of tics with ADHD, methylphenidate was better tolerated than dextroamphetamine,[3] but the mixed amphetamine compound has not been tested. Pemoline is used infrequently because of its potential for hepatotoxic reaction, but some clinicians assume that it will be safer in patients with a tic because there are fewer reports of adverse effects. However, the high incidence of severe abnormal involuntary movements (20%) in 1 series raises questions about its suitability in patients who have tics.[15]

Preliminary work with atypical neuroleptics for tic disorders suggests they will be effective if they have substantial D_2 dopamine antagonism.[16] A multisite randomized clinical trial is exploring the combination of methylphenidate and clonidine with a 2×2-factorial design (Roger Kurlan, MD, e-mail communication, December 11, 1998). Most intriguing is the work being done with nicotinic agents to potentiate neuroleptic effects.[17,18] In all of these cases, we can take comfort that data are increasingly replacing dogma.

F. Xavier Castellanos, MD
National Institute of Mental Health
Child Psychiatry Branch
10 Center Dr
Room 3B-19
MSC 1251
Bethesda, MD 20892-1251

REFERENCES

1. Lowe TL, Cohen DJ, Detlor J, Kremenitzer MW, Shaywitz BA. Stimulant medications precipitate Tourette's syndrome. *JAMA*. 1982;247:1729-1731.
2. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Grossman S. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry*. 1999;56:330-336.
3. Castellanos FX, Giedd JN, Elia J, Marsh WL, Ritchie GF, Hamburger SD, Rapoport JL. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry*. 1997;36:589-596.
4. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Arch Gen Psychiatry*. 1995;52:444-455.
5. Sverd J, Gadow KD, Paolicelli LM. Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1989;28:574-579.
6. Castellanos FX. Tic disorders and obsessive-compulsive disorder. In: Walsh BT, ed. *Child Psychopharmacology*. Washington, DC: American Psychiatric Press; 1998:1-28.
7. Golden GS. The effect of central nervous system stimulants on Tourette syndrome. *Ann Neurol*. 1977;2:69-70.
8. Pollack MA, Cohen NL, Friedhoff AJ. Gilles de la Tourette's syndrome: familial occurrence and precipitation by methylphenidate therapy. *Arch Neurol*. 1977;34:630-632.
9. Denckla MB, Bemporad JR, MacKay MC. Tics following methylphenidate administration: a report of 20 cases. *JAMA*. 1976;235:1349-1351.
10. Erenberg G, Cruse RP, Rothner AD. Gilles de la Tourette's syndrome: effects of stimulant drugs. *Neurology*. 1985;35:1346-1348.
11. Shapiro AK, Shapiro E. Do stimulants provoke, cause, or exacerbate tics and Tourette Syndrome? *Compr Psychiatry*. 1981;22:265-273.
12. Price RA, Leckman JF, Pauls DL, Cohen DJ, Kidd KK. Gilles de la Tourette's Syndrome: tics and central nervous system stimulants in twin and nontwins. *Neurology*. 1986;36:232-237.
13. Cohen DJ, Leckman JF. Commentary on "Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's Syndrome." *J Am Acad Child Adolesc Psychiatry*. 1989;28:580-582.
14. Bliss J. Sensory experiences of Gilles de la Tourette syndrome. *Arch Gen Psychiatry*. 1980;37:1343-1347.
15. Sallee FR, Stiller RL, Perel JM, Everett G. Pemoline-induced abnormal involuntary movements. *J Clin Psychopharmacol*. 1989;9:125-129.
16. Lombroso PJ, Scahill L, King RA, Lynch KA, Chappell PB, Peterson BS, McDougle CJ, Leckman JF. Risperidone treatment of children and adolescents with chronic tic disorders: a preliminary report. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1147-1152.
17. Sanberg PR, Silver AA, Shytle RD, Philipp MK, Cahill DW, Fogelson HM, McConville BJ. Nicotine for the treatment of Tourette's syndrome. *Pharmacol Ther*. 1997;74:21-25.
18. Sanberg PR, Shytle RD, Silver AA. Treatment of Tourette's syndrome with mecamylamine. *Lancet*. 1998;352:705-706.